16. (Amended) An *in vitro* process for the production of an immortalized, epithelial tumor cell comprising the step of incorporating DNA comprising DNA encoding at least one immortalizing oncogene into a non-immortalized epithelial tumor cell with metastatic potential, wherein said non-immortalized cell was disseminated from a primary tumor, has the phenotype of the primary tumor, and does not divide.

Kindly add the following claims:

39. (New) The epithelial tumor cell according to claim 1, which is a non-small cell lung cancer cell.

40. (New) The epithelial tumor cell according to claim 16, which is a non-small cell lung cancer cell.

REMARKS

Claims 1-12, 16-22, 29-31, 33-35, and 38-40 are pending in this application. Applicants would like to thank Examiner Harris and her SPE, Tony Caputa for speaking to applicants' representative, Jayme Huleatt, on February 12, 2003, during a telephone interview, to discuss the Examiner's the grounds of the rejection in the outstanding Office Action. Applicants acknowledge the Examiner's withdrawal of all of the rejections based on using Ohnuki *et al.* as the primary reference. Claims 1 and 16 are amended. Support for the amendments to claims 1 and 16 is found on page 2, lines 14-15 and lines 28-29 and page 4, lines 28-32. These claims have been amended to clearly define some of the characteristics of a cell with metastatic potential. Claim 2 is canceled without prejudice or disclaimer. Claims 39 and 40 are added and have support in amended claim 1 and in the detailed description of Figure 4, with reference to panel D, on page 17 of the specification. As there are no outstanding rejections of claim 35, it appears that claim 35 is allowable.

Rejection under 35 U.S. C. § 103

1. Claims 1-10, 16-22 and 38

Claims 1-10, 16-22 and 38 are rejected as allegedly obvious over the ATCC catalogue in view of Garcia *et al.* ("Garcia") and Chang *et al.* ("Chang"). The Examiner has replaced Ohnuki as the primary reference with the ATCC, which discloses a non-small cell lung cancer human tumor cell line, NCI-H1155 (ATCC CRL-5818) from a lymph node. The Examiner characterizes this cell line as having "metastatic potential." The Examiner admits

that this cells line does not teach that the cell has integrated into its genome or another replicative genetic element the DNA encoding the early region (large T antigen) of non-infectious SV40 DNA nor at least one additional oncogene. The Examiner admits that the ATCC does not disclose at least one defect in the origin of replication or the *in vitro* process by which the tumor cell incorporates the DNA encoding at least one immortalizing oncogene into a non-immortalized epithelial tumor cell. Additionally, the method step of microinjecting the DNA after primary expansion of the epithelial tumor cells is acknowledged by the Examiner as not being taught by the ATCC catalogue. The Examiner applies Garcia and Chang as she did in the final rejection mailed on October 22, 2001.

The Examiner states that it would be obvious to a person skilled in the art to use the ATCC cell line, CRL-5818, to establish a metastatic cell line suitable for studying the immortalizing and transforming potential of known and candidate genes for epithelial cells. As in that final rejection, the Examiner states that "[o]ne of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the ATCC catalogue, Garcia and Chang that the establishment of such a cell line could be readily made and successfully propagated in order to conduct experiments geared to the long term study of metastasis in many assay systems." The Examiner utilizes the same arguments and reasons to combine the three prior art references (ATCC catalogue, Garcia and Chang) as she did in the final rejection mailed on October 22, 2001 (Ohnuki, Garcia and Chang) with the exception that she has substituted the ATCC cell line for the cells disclosed in Ohnuki. The Examiner's basis for combining these prior art in the present Office Action is same as in the previous final rejection except for the substitution of the ATCC catalogue for Ohnuki.

Applicants respectfully traverse this rejection on the same grounds as has been argued again and again during the long and extended prosecution of the presently pending claims. The Examiner again has not met her burden of supporting a motivation to combine the cited prior art without using applicants' own disclosure as motivation. Applicants again point out that the Examiner has utilized impermissible hindsight to construct the present rejection based upon Applicants' own disclosure. When combining elements to make out a *prima facie* case of obviousness, the Examiner is obliged to show by reference to specific evidence in the cited references that there was (i) a suggestion to make the combination and (ii) a reasonable expectation that the combination would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*,

5 USPQ2d 1529, 1531 (Fed. Cir. 1988). The Examiner has failed to support the alleged case of *prima facie* obviousness.

Obviousness "'cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination.'" *In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988), *citing ACS Hosp. Sys. v. Montefiore Hosp.*, 221 USPQ 929, 933 (Fed. Cir. 1984). It is applicants' position that the combination of the prior art fails to provide a suggestion to make the present invention.

Specifically in regard to the teachings of the ATCC catalogue, all that is disclosed is a non-small cell carcinoma cell line derived by Gazdar and associates from a lymph node metastasis. The presently claimed cell is "an immortalized, epithelial tumor cell with metastatic potential" with specific characteristics. The ATCC catalogue discloses that NCI-H155 is obtained from a "lymph node metastasis." The specification of the present application on page 5, beginning at line 6, discloses that "metastatic potential" describes the potential of the epithelial tumor cell to be the nucleus of metastatic formation. The ATCC catalogue does not describe the NCI-H1155 cell as having metastatic potential but rather this cell is obtained from a metastases, and therefore, has gone beyond the "potential" and is actually a metastatic cell. The present specification on page 5, goes on to state that it is known that the first step in tumor formation is the generation of cell variants in the primary tumor which subsequently detaches from the tumor coenobium and proceeds after invasion and penetration of the stromal tissue to the lymph and blood vessel system. Further, the specification discloses on page 2, beginning at line 9, the present invention fulfills the need to identify epithelial tumor cells that are "prone to become the nucleus of a metastasis." This statement is interpreted to mean that the tumor cell has not yet become a metastatic cell but has the potential to become one. Further, this portion of the specification discloses that the tumor cells, which are suitable for use in an identification system, are those which have been disseminated from the primary tumor and that have infiltrated into a secondary tissue. Applicants believe that these arguments should be sufficient to distinguish the presently claimed cell from NCI-H1155 but in an effort to expedite the protracted prosecution of the present claims, claims 1 and 16 have been amended to further clarify the distinctions of the claimed tumor cell over the ATCC catalogue disclosed cell.

In an effort to provide additional background information regarding the NCI-H1155 cell line disclosed in the ATCC catalogue, a review of the ATCC catalogue shows that it references a publication by Giaccone *et al.* ("Giaccone" - a copy is enclosed for the Examiner's convenience). From a review of Giaccone, applicants note the identification of 4 NSCL cells, i.e., NCI-H460, NCI-H 810, NCI-H 1155 (the ATCC cell line cited in the present Office Action) and NCI-H 1341, in Table 1 but this publication remains silent regarding how the four non-small cell lung cancer cells are produced. On page 2732s, two publications, Carney *et al.* (cited by the Examiner in the Office Action dated March 15, 2001 as the primary reference in the obviousness rejection) and Lebacq-Verheyedn *et al* (a copy is enclosed for the Examiner's convenience) are referenced as the source of the "human lung cancer cell lines. A review of Carney shows that it only refers to NCI-H460 (See Table 5). The other three cell lines disclosed in Giaccone are not disclosed in Carney. Applicants previously presented arguments against Carney in their response of August 13, 2001, which in its pertinent part argued that Carney does not disclose non-small-cell lung cancer cells. Applicants refer the Examiner to page 3 of the response filed on August 13, 2001.

Further, applicants maintain that the NCI-H1155 cell line of the ATCC catalogue is not properly combinable with the teachings of Garcia and Chang. As argued in previous responses, Garcia does not disclose the transformation of a tumor cell but rather Garcia describes the transformation of a normal epithelial cell, and therefore the immortalization of a non-tumor cell. Furthermore, Garcia discloses the transformation of a rabbit cell by micro-injecting SV40 viral DNA and/or the human oncogene Ha-ras. In this regard, Garcia stresses on page 1980, left-hand column, first paragraph of discussion, second and third paragraphs:

> "When injected alone, these molecules were unable to transform rabbit mammary cells. The combination of SV40 DNA and activated c-Ha-ras gene, however, induced drastic changes in the micro-injected cells" (emphasis added)

In addition, on page 1974, right-hand column, last sentence of the introduction, Garcia points out:

> "An immortalized cell line obtained after injecting SV40 DNA into primary cells retained some but not all of the differentiation markers of mammary secretory cells from pregnant rabbits, whereas a cell line fully transformed by SV40 and the activated human c-Ha-ras DNA became tumorigenic." (emphasis added)

Therefore, Garcia teaches that tumorigenic cells can be obtained form normal epithelial cells by co-injecting SV40 and the human oncogene c-Ha-ras. There is simply no motivation to utilize the method of Garcia to introduce an immortalizing oncogene into the NCI-H1155 cells, which is already an immortalized tumor cell line.

In further support of the nonobviousness of the present invention, a review of Table 2 of previously cited Carney shows that SCLC negative cells cannot be used to establish cell lines and 75% of the SCLC positive cells are used to establish cell lines, showing that SCLC positive cells do not need Garcia's methods to become an immortal and to establish cell lines. Specifically, Carney provides evidence on page 2915, first column, first complete paragraph, that "[n]o cell lines were established from specimens pathologically and cytologically negative for SCLC tumor cells (Table 2)." This data shows that no cell lines were established for 184 bone marrow specimens that were SCLC negative, whereas cell lines were established from 12 of the 16 SCLC positive cells of the 200 tested bone marrow specimens. Thus, a skilled person in the art takes from Carney that tumor negative cells cannot be used to establish cell lines where as tumor positive cells can be used to establish cell lines without manipulating the tumor positive cells with techniques as taught by Garcia.

In contrast, the present invention documents a 10,000 fold transient expansion of early disseminated epithelial tumor cell, (see page 28, Example 8). The disclosed amplification of the present invention, therefore, allows the establishment of cell lines from bone marrow samples which would have been classified as "tumor-free" by conventional methods employed in Carney.

As previously argued, Chang adds nothing to the Examiner's rejection except the disclosure of basic protocols for SV40 infections. Again, this reference as argued on pages 4 and 5 of the previous response does not provide for an immortalized, non-small cell lung cancer epithelial tumor cell or a method to generate such a cell.

The present invention provides immortalized non-SCLC epithelial tumor cells that are derived from the earliest metastasizing cells which have conserved the phenotype of the residual tumor cells present in the patient. See the paragraph bridging pages 4 and 5 of the specification. It is important to recognize these cells at this very early stage and generate quantities of them to analyze the early stages of cancer for identification and therapeutic methods. Accordingly, the cells of the present invention are clearly distinct from the

metastatic cell described in the ATCC catalogue Therefore, the skilled artisan would not have combined the ATCC catalogue disclosure with Garcia and Chang to arrive at the claimed immortalized non-SCLC epithelial tumor cells which express an immortalizing oncogene, and particularly, the process of making this immortalized tumor cells.

Applicants respectfully disagree with the Examiner's rationale for combining the cited prior art and for utilizing impermissible hindsight to construct the present rejection based upon Applicants' own disclosure. It is applicants' position that the combination of the prior art fails to provide a suggestion to make the present invention. For all of the reasons and all of the arguments presented above, this rejection should be withdrawn.

2. Claims 1-12, 16-22, 29, 30 and 38

Claims 1-12, 16-22, 29, 30 and 38 are alleged to be obvious over the ATCC catalogue ("ATCC") in view of Garcia *et al.* ("Garcia"), Blankenstein *et al.* ("Blankenstein") and Chang *et al.* ("Chang"). The Examiner applies ATCC as above and Garcia, Chang and Blankenstein as in the previous final rejection. The addition of Blankenstein fails to cure the deficiencies in the primary references, and in view of the above arguments directed to the combination of the primary references, it is requested that this rejection be withdrawn.

3. Claims 1-10, 16-22, 31 and 38

Claims 1-10, 16-22, 31 and 38 are alleged to be obvious over the ATCC catalogue ("ATCC") in view of Garcia *et al.* ("Garcia"), and the Sigma Cell Cutlure Catalogue and Price List ("Sigma"). The Examiner applies the ATCC and Garcia as above, and Sigma to teach to availability of growth factor supplements for use in the culture medium. The addition of Sigma fails to cure the deficiencies in the primary references, and in view of the above arguments directed to the combination of the primary references, it is requested that this rejection be withdrawn.

4. Claims 1-10, 16-22, 33, 34 and 38

Claims 1-10, 16-22, 33, 34 and 38 are alleged to be obvious over the ATCC catalogue ("ATCC") in view of Garcia *et al.* ("Garcia") and Gottlinger *et al.* ("Gottlinger"). The Examiner applies the ATCC and Garcia, as above and Gottlinger to teach to epithelial surface antigens and adjuvants suitable for mounting an immunological response. The addition of

Gottliner fails to cure the deficiencies in the primary references, and in view of the above arguments, it is requested that this rejection be withdrawn.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they solicit an early indication to that effect. Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, a telephone call to the undersigned, at the telephone number listed below, is courteously invited.

Respectfully submitted,

March 21, 2003
Date

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Marked-up version of claims:

1. (Amended) An immortalized[non-small cell lung cancer], epithelial tumor cell with metastatic potential which has integrated in its genome or another replicative genetic element an externally introduced immortalizing oncogene which is expressed in said cell**, wherein said cell was disseminated from a primary tumor, has the phenotype of the primary tumor, and prior to the introduction of said immortalizing oncogene said cell does not divide**.

16. (Amended) An *in vitro* process for the production of [the] **an immortalized, epithelial** tumor cell [according to claim 1] comprising the step of incorporating DNA comprising DNA encoding at least one immortalizing oncogene into a non-immortalized epithelial tumor cell with metastatic potential**, wherein said non-immortalized cell was disseminated from a primary tumor, has the phenotype of the primary tumor, and does not divide**.